REMARKS

Claims 23, 28 and 68 have been amended. Claims 48-53, 55, 59-62 and 64-67 are reiterated, and claims 69-77 have been added. Claims 1-22, 24-27, 29-47, 54, 56-58 and 63 were previously canceled. Upon entry of this amendment, claims 23, 28, 48-53, 55, 59-62, and 64-77 will be pending.

Support for the amendments to claims 23, 28 and 68, and new claim 77 can be found in Figures 2-4, and in Example 6 at pages 28-30 of the original specification. Support for newly added claim 77 can also be found, *e.g.*, at page 14, line 29. No new matter has been added.

Applicants note with appreciation the examiner's reconsideration and withdrawal of some of the aspects of the rejection of the claims for obviousness-type double patenting and under 35 U.S.C. § 103.

It is noted that the priority date for the present application is December 14, 1998 in view of Applicants' request and the correction to the specification.

Rejection of Claims 23, 28, 48, 55, 59, and 64 for Obviousness-Type Double Patenting

Claims 23, 28, 48, 55, 59, and 64 are rejected as being unpatentable allegedly for obviousness-type double patenting over claims 1, 6-8 and 14 of Collins *et al.*, U.S. Patent No. 6,248,714 ("the '714 patent") in view of Cookson *et al.*, U.S. Patent No. 6,387,615 ("the '615 patent") and Hamelmann *et al.* (*Allergy and Clinical Immunology International, Abstract*, Vol. 10/2:59-63, 1998; "Hamelmann").

To support this rejection, the Office states that:

> The claims of the '714 patent do not teach allergen-induced airway hyper responsiveness. Cookson et al. teach that asthma in children and young adults in initiated by IgE-mediated allergies to inhaled allergens. Hamelmann et al. teach experiments directed at treating airway hyper responsiveness (AHR) in bronchial asthma. The prior art of record teach that asthma is initiated by IgE-mediated allergies and that asthma is characterized by allergen induced airway hyper responsiveness. The genus of treating an Ig-mediated condition, as claimed in the '741 patent, renders the species of IgE mediated condition such as allergen-induced airway hyper responsiveness, obvious. Lastly, the claims of the '714 patent

broadly encompasses any mode of administration (genus) and thus renders the modes of administration (species) as recited in instant claim 68, obvious.

As the Office is aware, a double patenting rejection is based on a comparison of the claims in the reference patent or application and the pending claims in the application being examined (M.P.E.P. 1504.06). To establish a *prima facie* case of obviousness-type double patenting, the difference in scope between the claims being compared is minor and patentably indistinct (M.P.E.P. 1504.06, section II).

The present rejection is respectfully traversed. As explained in more detail below, the presently claimed methods are directed to the treatment of non-obvious and patentably distinct conditions, such as allergen-induced airway hyper responsiveness and/or increase in mucus-containing cells in the airway epithelium, which were not obvious or would have been reasonably expected in view of the broad teaching of treatment of asthma in the claims of the '714 patent in combination with the secondary references.

Pending claims 23 and 28 are directed to methods of reducing, or treating, an allergen-induced airway hyper responsiveness or an allergen-induced increase in mucus-containing cells, in a subject, by administering to the subject a particular IL-13Rα2 polypeptide or a sequence homologous thereto in an amount sufficient to reduce or treat the hyper responsiveness or the increase in the mucus-containing cells. Similarly, claim 68 and claims dependent therefrom are directed to methods of administering the aforesaid IL-13Rα2 polypeptides to a mammalian subject having an allergen-induced airway hyper responsiveness or an allergen-induced increase in mucus-containing cells. Newly added claim 77 is directed to a method of treating an inflammatory condition of the lung characterized by allergen-induced airway hyper responsiveness and an increase in mucus-containing cells in the airway epithelium in a mammalian subject by administering the aforesaid IL-13Rα2 polypeptides.

The claims of the '714 patent are directed to methods of inhibiting the binding of IL-13 to the IL-13 receptor, or treating an Ig-mediated condition (*e.g.*, IgE-mediated

conditions, such as an allergic condition, asthma, or an immune complex disease) using the amino acid sequence from the IL-13 receptor α2 specified or a portion thereof.

As acknowledged by the Office, the claims of the '714 patent do not teach treatment of allergen-induced airway hyper responsiveness (Office Action, page 7). Similarly, the '714 claims do not teach treatment of an allergen-induced increase in mucus-containing cells in the airway epithelium or lung inflammation, as newly introduced to the claims. The Office cites Cookson et *al.* and Hammelmann *et al.* as supporting the proposition that "asthma is initiated by IgE-mediated allergies and that asthma is characterized by allergen-induced airway hyper responsiveness."

Applicants respectfully disagree with the Office's characterization of Cookson *et al.* and Hammelmann *et al.* Applicants' invention provides conclusive evidence that antagonism of IL-13 alone using, *e.g.*, soluble fusion of the IL-13Rbc, ameliorates airway hyper responsiveness and mucus-secretion *in vivo* (Example 6 of specification). In fact, Example 6 shows that antagonism of IL-13 leads to complete reversal of airway hyper responsiveness and mucus-secretion *in vivo*. This finding was surprising at the time the present application was filed given the multiple responses and often redundant signaling pathways triggered by IL-13 *in vivo*. Based on the combination of secondary references cited by the Office, one of ordinary skill in the art would not have expected that antagonism of IL-13 could have ameliorated *in vivo* the particular conditions recited by the claims, namely, airway hyper responsiveness, mucus-secretion and/or pulmonary inflammation. There are many pathways with ultimate *in vivo* responses that could have been affected by inhibition of IL-13 that would not have involved inhibition of airway hyper responsiveness, mucus production, or lung inflammation. Two examples of such pathways (*i.e.*, modulation of IgE levels and/or eosinophilia) are provided by the secondary references cited by the Office. Other examples are provided in the background of the instant application where it is described that IL-13 was known in the art to be associated with several biological activities such as (i) induction of IgG4 and IgE switching, including in human immature B cells; (ii) induction of germ line IgE heavy chain (e) transcription and CD23 expression in normal B cells; and (iii) induction of B

cell proliferation in the presence of CD40L or anti-CD40 mAb (see background of the specification at page 1, lines 20-25). In view of the numerous pathways implicated in IL-13 activities *in vivo*, one of ordinary skill in the art would not have expected that blockade of IL-13 would have led particularly to amelioration of airway hyper responsiveness, mucus-secretion, and/or pulmonary inflammation *in vivo* based on the disclosures of the secondary references.

More particularly, the Cookson reference cited by the Office provides that:

> Asthma is a disease which is becoming more prevalent and is the most common disease of childhood (Ref. omitted). Most asthma in children and young adults is initiated by IgE mediated allergy (atopy) to inhaled allergens such as house dust mite and cat dander. **However, not all asthmatics are atopic, and most atopic individuals do not have asthma. Thus, factors in addition to atopy are necessary to induce the disease** (Ref. omitted). Asthma is strongly familial, and is due to the interaction between genetic and environmental factors. The genetic factors are thought to be variants of normal genes ("polymorphisms") which alter their function to predispose to asthma. (US 6,387,615, column 1, lines 13-24 (emphasis added))

In fact, the Cookson reference is primarily concerned with genetic polymorphisms in or linked to the TNFα gene that are predictive of asthma, and their uses as diagnostic and prognostic tools. Therefore, unlike the Office's position that the Cookson reference teaches that "asthma in children and young adults is initiated by IgE-mediated allergies," this reference quickly clarifies that other factors, such as genetic and environmental factors, are necessary to induce the disease. This reference says nothing about the role of an inflammatory cytokine such as IL-13 in ameliorating airway hyper responsiveness, mucus-secretion and/or lung inflammation *in vivo*. At best, it teaches that genetic polymorphisms in or linked to the TNFα gene are predictive of asthma, thus suggesting a genetic predisposition to asthma.

The Office also cites Hammelman *et al.* as disclosing "experiments directed at treating airway hyper responsiveness in bronchial asthma." This reference, however, concerns the characterization of antagonism of IL-5 as a therapy for disorders having an inflammatory component, such as AHR, in atopic, bronchial asthma. This reference, in

fact, makes a distinction between IgE-related disorders, such as allergic rhinitis for which anti-IgE therapy would be more beneficial, and inflammatory disorders for which IL-5 antagonism would be preferred. The Hammelman reference is completely silent with respect to the effects of antagonizing IL-13 to treat either IgE-related or inflammatory disorders. In fact, the reference unambiguously encourages one of ordinary skill in the art to antagonize IL-5 for treating inflammatory conditions, as follows:

> Based on these studies, we conclude that IL-5 is a **pivotal factor** in the development of airway inflammation and AHR, and that IgE plays an important contributing role under conditions in which limited IL-5-mediated eosinophilic airway infiltration is induced. In conditions where a robust eosinophilic inflammation of the airways is elicited, IL-5 but not IgE appears to be **essential** for airway inflammation and the development of AHR. (Hamelmann, E. *et al.* (1998) *ACI International*, 10/2, page 63, emphasis added).

In fact, a contemporaneous publication by the same authors provides that:

> As well as elevated serum IgE levels, eosinophilic airway inflammation is regularly observed in bronchial asthma (Ref. omitted)… The main growth, differentiation, and survival factor for eosinophils is IL-5 (Ref. omitted) and, indeed, IL-5 **has been shown to be essential** for the induction of allergen-induced eosinophilic airway inflammation in most studies in mice (Ref. omitted) and guinea pigs (Ref. omitted). We previously demonstrated that treatment of high IgE-responder BALB/c mice with anti-IL-5 during airway sensitization **completely prevented the development of AHR, despite production of allergen-specific IgE and immediate cutaneous hypersensitivity, suggesting a dissociation between elevated IgE serum levels on the one hand and airway inflammation and AHR on the other** (Ref. omitted). …
>
> We show that treatment of allergen-sensitized mice with **anti-IgE antibody** reduces total and allergen-specific IgE serum levels and prevents development of (cutaneous and systemic) anaphylactic reactions, **but has little effect** on airway inflammation or development of AHR. In contrast, anti-IL-5 treatment of such mice inhibits eosinophilic airway inflammation and development of AHR. (Hammelman, E. *et al.* (1999) *Am J Repir Crit Care Med* Vol 160, pages 934-935, emphasis added, submitted herewith as Exhibit A).

Thus, the passages from the Hammelman references quoted above make a clear distinction between conditions associated with elevated IgE levels, the decrease of which

has "little effect on airway inflammation or development of AHR," and anti-inflammatory therapies involving IL-5 antagonism, which "inhibits eosinophilic airway inflammation and development of AHR." *Id.* The Hammelman references are completely silent about the effects of IL-13 or antagonism of IL-13, or whether antagonism of IL-13 could be used block elevated IgE levels, as an anti-inflammatory or an anti-eosinophilic therapy, or as any therapy.

It is important to emphasize that even though a decrease in IgE levels has "little effect on airway inflammation or development of AHR" in the Hammelman reference, Xolair®, an anti-IgE therapy, is clinically approved to treat moderate to severe allergic asthma. Therefore, asthmatic disorders can be treated with a wide range of therapeutic approaches, such as anti-IgE, anti-eosinophilic, and anti-inflammatory therapies, to name a few. A broad teaching that antagonism of IL-13 can be used to treat asthma would not have suggested, or provided a reasonable expectation, to one of ordinary skill in the art at the time the application was filed that blockade of IL-13 would ameliorate airway hyper responsiveness, mucus secretion and/or lung inflammation, as presently claimed. The secondary references cited by the Office fail to provide the requisite motivation and reasonable expectation of success as these references simply teach that asthma is a multi-factorial disorders having environmental and genetic components (the Cookson reference) and encourage the use of anti-IL5 therapy to reduce airway hyper responsiveness (Hammelman *et al.*).

In view of the foregoing comments, reconsideration and withdrawal of the rejection for obviousness-type double patenting are respectfully requested.

Rejections of Claims, 23, 28, 48-53, 55, 59, and 64-67 under 35 USC § 103(a)

Claims 23, 28, 48-53, 55, 59, and 64-67 are rejected as unpatentable under 35 USC §103(a) over Collins *et al.*, U.S. Patent No. 5,710,023 ("the '023 patent"), or U.S. Patent No. 6,268,480 ("the '480 patent"), or U.S. Patent No. 6,214,559 ("the '559 patent"), in view of Cookson *et al.*, the '615 patent and Hamelmann *et al.* (*Allergy and Clinical Immunology International, Abstract*, Vol. 10/2:59-63, 1998), both of which were

discussed above. Since the patents by Collins *et al.* (referred to collectively herein as the "Collins patents") cited by the Office have similar disclosures (as they are related to each other as divisional applications), all of these patents are discussed together herein.

According to the Office:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify a method of treating asthma by administering IL-13bc as taught by Collins et al. to treat allergen-induced airway hyper responsiveness with a reasonable expectation of success. The motivation and expected success is provided by Collins et al., Cookson et al and Hamelmann et al. Collins et al, teach a mechanism for inhibiting the binding of IL-13bc. Collins et al. teach that the method can be used in the treatment of asthma. Cooke et al. teach that asthma is initiated by IgE-mediated allergies. Hamelmann et al. teach that asthma is characterized by AHR. Since asthma is characterized by AHR, it would be obvious to use the method of Collins et al. to treat AHR. (Office Action, page 10).

Pending claims 23 and 28 (and claims dependent therefrom) are directed to methods for reducing, or treating, an allergen-induced airway hyper responsiveness or an allergen-induced increase in mucus-containing cells, in a subject, by administering to the subject a particular IL-13Rα2 polypeptide or a sequence homologous thereto in an amount sufficient to reduce or treat the hyper responsiveness or the increase in the mucus-containing cells. Similarly, claim 68 and claims dependent therefrom are directed to methods of administering the aforesaid IL-13Rα2 polypeptides to a mammalian subject having an allergen-induced airway hyper responsiveness or an allergen-induced increase in mucus-containing cells. Newly added claim 77 is directed to a method of treating an inflammatory condition of the lung characterized by allergen-induced airway hyper responsiveness and an increase in mucus-containing cells in the airway epithelium in a mammalian subject by administering the aforesaid IL-13Rα2 polypeptides.

The Collins patents neither teach nor suggest treatment of allergen-induced airway hyper responsiveness nor allergen-induced increase in mucus-containing cells in a subject upon administration of an IL-13Rα2 polypeptide. The broad teaching in Collins of treatment of asthma quoted by the Office would not have led, or provided a reasonable expectation to, one of ordinary skill in the art at the time of filing that blockade of IL-13

would ameliorate airway hyper responsiveness, mucus secretion and/or lung inflammation *in vivo*, as presently claimed. There are many pathways with ultimate *in vivo* responses that could be affected by inhibition of IL-13. More specifically, IL-13 was known in the art at the Applicants' filing date to be associated with multiple biological activities such as (i) induction of IgG4 and IgE switching, including in human immature B cells; (ii) induction of germ line IgE heavy chain (e) transcription and CD23 expression in normal B cells; and (iii) induction of B cell proliferation in the presence of CD40L or anti-CD40 mAb. In view of the numerous pathways implicated in IL-13 activities *in vivo*, one of ordinary skill in the art would not have expected that blockade of IL-13 would have led particularly to amelioration of airway hyper responsiveness, mucus-secretion, and/or pulmonary inflammation *in vivo*, as presently claimed.

The secondary reference of Cookson *et al.* fails to make up for the deficiencies in the Collins patents. The Cookson reference is primarily concerned with genetic polymorphisms in or linked to the TNFα gene, which are predictive of asthma, and their uses as diagnostic and prognostic tools. Therefore, unlike the Office's position that the Cookson reference teaches that "asthma in children and young adults is initiated by IgE-mediated allergies," this reference clarifies that other factors, such as genetic and environmental factors, are necessary to induce the disease. This reference says nothing about the role of an inflammatory cytokine, such as IL-13, in reducing airway hyper responsiveness, mucus-secretion and/or lung inflammation *in vivo*. At best, it teaches that genetic polymorphisms in or linked to the TNFα gene are predictive of asthma, thus suggesting a genetic predisposition to asthma.

Indeed, airway hyper responsiveness has been described in some references as being uncoupled from the IgE levels. This is described by Applicants, *e.g.*, as stated at page 29 of the specification:

> Nonetheless, these results show that AHR [airway hyper responsiveness] is not dependent upon IgE production in this model, consistent with reports that allergic AHR develops normally in IgE deficient and B cell deficient mice. (emphasis added)

In addition, although eosinophils were known at the time of filing to be primary effector cells for asthmatic airway hyper responsiveness (see the Hammelman reference cited by the Office), inhibition of IL-13 did not significantly affect allergen-induced pulmonary eosinophilia (see specification at page 29, lines 12-16 and Figure 2B). Therefore, prior to the present invention, one of ordinary skill in the art would not have been able to predict that antagonism of IL-13 would have resulted in the reduction of airway hyper responsiveness and the allergen-induced increase in mucus-containing cells *in vivo*, as presently claimed.

The Hamelman reference does not cure the deficiencies of the Collins patent, alone or in combination with the Cook reference. The Hamelman reference discloses antagonism of IL-5 as a therapy for disorders having an inflammatory component, such as AHR, in atopic bronchial asthma. This reference simply makes a distinction between IgE-related disorders, such as allergic rhinitis, for which anti-IgE therapy would be more beneficial, and inflammatory disorders, for which IL-5 antagonism would be preferred. The Hammelman reference is completely silent with respect to the effects of antagonizing IL-13 to treat either IgE-related or inflammatory disorders, let alone in reducing airway hyper responsiveness, mucus-secretion and/or lung inflammation *in vivo*.

The Hamelmann reference discloses that the role of cytokines in airway hyper responsiveness is "…not well defined and requires further delineation," as follows:

> In contrast to the recognized importance of IgE in the induction of immediate allergic responses, the role of cytokines and IgE in chronic allergic airway inflammation and AHR **is not well defined and requires further delineation**. Since patients suffering from allergic airway disease often demonstrate parallel increases in IgE, Th2-type cytokines, and airway eosinophils, it is difficult to evaluate the interrelationship or importance of any one of these factors in the induction of airway inflammation and AHR.
> (Hamelmann reference, page 59, right-hand column, emphasis added)

Hamelmann concludes by stating that IL-5 is a key factor in the development of airway inflammation and AHR, and suggests that anti-IL-5 therapy would be beneficial in the treatment of AHR (see Hamelmann at page 63, left column). In fact, the reference

unambiguously encourages one of ordinary skill in the art to antagonize IL-5 for treating inflammatory conditions of the lung.

Therefore, the Collins patents, alone or in combination with the secondary references cited by the Office fail to provide the requisite motivation and reasonable expectation of success to one of ordinary skill in the art that blockade of IL-13 would ameliorate airway hyper responsiveness, mucus secretion and/or lung inflammation, as presently claimed.

In view of the foregoing comments, reconsideration and withdrawal of the rejection under 35 USC § 103(a) are respectfully requested.

CONCLUSION

Applicants submit that the application is in condition for allowance, and such action is respectfully requested. Please charge and payments or credit any overpayments of the same to Deposit Account No. 50-2762 referencing Attorney Docket No. W2023-7013US.

Respectfully submitted,

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